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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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909	7590	04/13/2004	EXAMINER	
PILLSBURY WINTHROP, LLP			RAMIREZ, DELIA M	
P.O. BOX 10500			ART UNIT	
MCLEAN, VA 22102			PAPER NUMBER	
			1652	

DATE MAILED: 04/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/963,668	<b>Applicant(s)</b> RIEPING ET AL.	
	<b>Examiner</b> Delia M. Ramirez	<b>Art Unit</b> 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 29 December 2003.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1,2,4-7 and 9 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1,2,4-7 and 9 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 December 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All    b) ☐ Some \*    c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                    | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____  |

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## **DETAILED ACTION**

### ***Status of the Application***

Claims 1-2, 4-7, 9 are pending.

Applicant's amendment of claims 1-2, 4-7, 9, cancellation of claims 3, 8, 10-27, and amendments to the specification in a communication filed on 12/29/2003 are acknowledged.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Drawings***

1. The formal drawings submitted 12/29/2003 are acknowledged and approved by the Examiner.

### ***Claim Objections***

2. Claim 6 is objected to due to the recitation of "from the group consisting of: 6.1...., (a)...., (b)...., (c)...., and (g)". It appears that the term "6.1" is a typographical error and should be replaced with "(a)". The terms "(a)", "(b)"..., and "(g)" should be replaced with "(b)", "(c)", "(d)"..., and "(h)", respectively. For examination purposes, the suggested language will be used. Appropriate correction is required.
3. Claim 2 is objected to due to the recitation of "other genes of the biosynthetic pathway of the desired L-amino acid of E. coli". For clarity, it is suggested that the term be amended to recite "other E. coli genes of the biosynthetic pathway of the desired L-amino acid". Appropriate correction is required.
4. Claim 9 is objected to due to the recitation of "process according to claims". It is suggested that the term be replaced with "process according to any one of claims" to ensure that claim 9 refers back to other claims in the alternative. Appropriate correction is required.

***Claim Rejections - 35 USC § 112***

5. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

6. Claims 4 and 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

7. Claim 4 is indefinite in the recitation of “the process according to claim 1, wherein the expression of the pckA gene is attenuated” for the following reasons. Claim 1 as amended recites “wherein the endogenous gene encoding phosphoenolpyruvate (PEP) carboxykinase (pckA gene) of E. coli is attenuated”. Therefore, it is unclear how the term “wherein the expression of the pckA gene is attenuated” further limits claim 1. For examination purposes, claim 4 will be considered a duplicate of claim 1. Correction is required.

8. Claim 9 is indefinite in the recitation of “the process according to claims 1 to 7 wherein L-isoleucine, L-valine, L-lysine, or L-threonine is prepared” for the following reasons. First, the claim depends on cancelled claim 3. In addition, it is unclear as to how this claim further limits any one of claims 1, 2, 4, 5, 6, or 7 since these claims are already directed to the production of L-isoleucine, L-valine, L-lysine, or L-threonine. See preamble of claim 1. For examination purposes, claim 9 will be considered a duplicate of claim 1. Correction is required.

***Claim Rejections - 35 USC § 112, First Paragraph***

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-2, 4-7 and 9 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in

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the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in Paper No. 11, mailed on 7/29/2003 and is maintained for the reasons of record and those set forth below.

11. Applicants argue that the claims as amended are directed to a process for the production of amino acids for which there is adequate description. Similarly, Applicants argue that the E. coli genes recited in the claims have been previously acknowledged by the Examiner as sufficiently described in the specification. Applicants also submit that claim 3 is now directed to the process according to claim 1 wherein the metabolic pathways which reduce the formation of the desired L-amino acid are at least partially switched off. Thus, it is Applicant's opinion that the amended claims are adequately described.

12. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejections of claims 1-2, 4-7 and 9. For the record, it is noted that claim 3 has been canceled. While it is agreed that the claims are now limited to E. coli genes, and specific amino acids produced, the Examiner disagrees with Applicant's contention that the claims are adequately described for the following reasons. Claims 1-2, 4-7 and 9 are directed to a fermentation process wherein the E. coli pckA gene is attenuated. According to the specification, the term "attenuation" encompasses the use of a gene or allele which codes for an appropriate enzyme with low activity (page 2, lines 25-30). While an inactivating deletion has been taught in regard to the pckA gene, the specification fails to disclose which mutations in the E. coli pckA gene can be made such that the gene product is one with low activity, i.e. one with less activity than the wild type counterpart. Claim 2 is directed to the process of claim 1 and also requires amplification of any E. coli gene associated with the biosynthetic pathway of L-threonine, L-isoleucine, L-valine, or L-lysine. The specification discloses the term "amplification" as encompassing the use of a gene coding for an appropriate enzyme or protein with a high activity, (page 8, lines 22-28). However, the specification fails to disclose which mutations in said genes would result in a gene product with high

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activity, i.e. one with higher activity than the wild-type counterpart. Furthermore, the specification is completely silent as to which *E. coli* genes are associated with the biosynthetic pathways of the desired amino acids or their structures. Claim 5 is directed to the process of claim 1 with the added limitation that the *E. coli* *pckA* gene product has regulatory and/or catalytic properties reduced. However, the specification fails to provide the structural changes in the *E. coli* *pckA* gene which would result in a gene product with reduced regulatory and/or catalytic properties. Claim 7 is directed to the process of claim 1 with the added limitation that specific *E. coli* genes are attenuated. As indicated above, attenuation according to the specification encompasses using genes which encode proteins with low activity. While the specification/prior art teaches the use of inactivating deletions for inactivating a protein, the specification fails to provide any teachings as to which are the structural changes in those specific *E. coli* genes which can be made such that the gene product is less active than the wild-type counterpart. Therefore, for the reasons set forth above and those discussed in a previous Office Action, one cannot reasonably conclude that the claimed invention is adequately described.

13. Claims 1-2, 4-7 and 9 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for (1) a fermentation process for the preparation of L-threonine, L-lysine, L-isoleucine or L-valine using an *E. coli* cell modified such that the *E. coli* *pckA* gene containing an inactivating deletion, (2) the process of (1) wherein the copy number of the following *E. coli* genes: *thr* ABC operon, *pyc*, *pps*, *ppc*, *pntA*, *pntB*, *rhtB*, *rhtC*, or *gdhA* is increased or wherein said *E. coli* genes are placed under the control of a strong promoter, (3) the process of (1) wherein the following *E. coli* genes: *tdh*, *mdh*, open reading frame *yjfA*, or open reading frame *yjfP* contain an inactivating deletion, does not reasonably provide enablement for (a) a fermentation process for the preparation of L-threonine, L-lysine, L-isoleucine or L-valine using an *E. coli* cell modified in any way such that the *E. coli* *pckA* gene product is less active than its wild-type counterpart, (b) the process of (a)

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wherein any E. coli gene associated with the biosynthetic pathway of L-threonine, L-lysine, L-isoleucine or L-valine is modified in any way to produce a protein which has higher activity than the wild-type counterpart, (c) the process of (a) wherein the pckA gene is modified in any way such that regulatory and/or catalytic properties of the pckA gene product are reduced, or (d) the process of (a) wherein the gene products of the E. coli tdh gene, E. coli mdh gene, E. coli open reading frame yjfA, or E. coli open reading frame yjfP are modified in any way such that these gene products are less active than their wild-type counterparts. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. This rejection has been discussed at length in Paper No. 11, mailed on 7/29/2003 and is maintained for the reasons of record and those set forth below.

14. Applicants argue that claims 1-7 and 9 as amended are directed to a process for the production of specific amino acids for which there is enablement. Similarly, Applicants argue that the E. coli genes recited in the claims have been previously acknowledged by the Examiner as enabled. Thus, it is Applicant's opinion that the amended claims are enabled by the teachings of the specification.

15. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. As indicated above, claim 3 has been canceled. It is reiterated herein that while the Examiner agrees that the claims are now limited to specific amino acids and E. coli genes, claims 1-2, 4-7 and 9 are directed to a fermentation process which requires the use of a mutated E. coli pckA gene wherein said gene encodes a protein with less activity than that of the wild type counterpart. See discussion above regarding the definition of "attenuation" as described in the specification. Furthermore, claim 2 requires the use of any E. coli gene associated with the biosynthesis of specific amino acids, wherein said gene has been mutated such that the corresponding protein has higher activity than the wild-type counterpart. See discussion above regarding the definition of "amplification". Claim 5 requires a mutated E. coli pckA gene encoding a gene product which has reduced regulatory and/or catalytic

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properties. Claim 7 requires specific *E. coli* genes which have been mutated such that their gene products have lower activity than their wild-type counterparts. While inactivating deletions are known in the art to inactivate a protein, the specification fails to disclose (1) which mutations in the *E. coli* *pckA* and the *E. coli* genes recited in claim 7 can be made such that the gene products have less activity than the wild type counterparts, (2) which mutations in any *E. coli* gene associated with the biosynthesis of the amino acids recited would result in a gene product with higher activity than the wild-type counterpart, (3) which *E. coli* genes are associated with the biosynthetic pathways of the desired amino acids, or their structures, or (4) the structural changes in the *E. coli* *pckA* gene which would result in a gene product with reduced regulatory and/or catalytic properties. Therefore, for the reasons set forth above and those discussed in a previous Office Action, one cannot reasonably conclude that the specification is enabling for the full scope of the claims.

***Claim Rejections - 35 USC § 103***

16. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

17. Claims 1, 4, 5, and 9 were rejected under 35 U.S.C. 103(a) as being unpatentable over Eikmanns et al. (U.S. Patent No. 6420151, filed on 12/7/1999) in view of Medina et al. (J. Bacteriol. 172(12):7151-7156, 1990; cited in the IDS), Goldie et al. (J. Bacteriol. 141(3):1115-1121, 1980; cited in the IDS), and Applicant's admission of the state of the art on page 1, lines 11-15 of the specification.

18. Claims 2 and 6 were rejected under 35 U.S.C. 103(a) as being unpatentable over Eikmanns et al. (U.S. Patent No. 6420151, filed on 12/7/1999) in view of Medina et al. (J. Bacteriol. 172(12):7151-7156, 1990; cited in the IDS), Goldie et al. (J. Bacteriol. 141(3):1115-1121, 1980; cited in the IDS), Applicant's admission of the state of the art on page 1, lines 11-15 of the specification, and further in view of Katinka et al. (Proc. Natl. Acad. Sci. 77(10):5730-5733, 1980; GenBank accession number V00361).



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19. In view of Applicant's statement in the Remarks section of the response filed on 12/29/2003 (page 13) indicating that U.S. Patent No. 6420151 (Eikmanns et al.) and the instant application were commonly owned at the time the presently claimed invention was made, the teachings of Eikmanns et al. are no longer proper prior art against claims 1, 2, 4, 5, 6 and 9. Since neither Medina, Goldie or Katinka teach the claimed invention alone or in combination, these rejections are hereby withdrawn.

***Double Patenting***

20. Claims 1, 4, 5 remain rejected and amended claim 9 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9-10 of copending Application No. 10/076416 (common inventors Mechthild Rieping and Georg Thierbach).

21. Claims 1, 4, 5 remain rejected and amended claim 9 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14 of copending Application No. 10/114043 (common inventors Mechthild Rieping and Thomas Hermann).

22. Claims 1, 4, 5 remain rejected and amended claim 9 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14 of copending Application No. 10/114048 (common inventors Mechthild Rieping and Thomas Hermann).

23. Claims 1, 4, 5 remain rejected and amended claim 9 is provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-14 of copending Application No. 10/114073 (common inventors Mechthild Rieping and Thomas Hermann).

24. Applicants argue that the claims have been amended to be directed to a fermentation process for the preparation of L-threonine, L-isoleucine, L-valine, or L-lysine by fermenting an E. coli strain with an attenuated pckA gene or a pckA gene wherein its expression is reduced. As such, it is Applicant's conclusion that the instant claims are patentably distinct and cannot be either anticipated or considered obvious over the disclosures of U.S. Patent No. 10/076416, 10/114043, 10/114048, or 10/114073.

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25. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejections. It is noted that amended claim 9 has been included in the list of claims rejected under the judicially created doctrine of obviousness-type double patenting as it has been interpreted as a duplicate of claim 1. Claim 4 has been interpreted as being a duplicate of claim 1. See above for claim interpretation. While it is agreed that the claims as amended are limited to an E. coli cell and specific amino acids, claims 12-14 of copending applications No. 10/114073, 10/114043, and 10/114048 and claims 9-10 of copending application 10/076416 render the instant claims obvious for the reasons of record and the following reasons. With regard to copending Application No. 10/076416 (U.S. Publication No. 20030017554), it is noted that the specification in this application discloses practicing the claimed process for the production of L-threonine, L-valine and L-lysine with an E. coli cell as one of the preferred embodiments. See paragraphs 17-33 and Example 4. As such, claims 1, 4-5 and 9 of the instant application would be considered obvious over claims 9-10 of copending Application No. 10/076416. With regard to copending Application No. 10/114043 (U.S. Publication No. 20030054503), it is noted that the specification in this application discloses practicing the claimed process for the production of L-threonine with an E. coli cell as one of the preferred embodiments. See paragraphs 36-52 and Example 4. As such, claims 1, 4-5 and 9 of the instant application would be considered obvious over claims 12-14 of copending Application No. 10/114043. With regard to copending Application No. 10/114048 (U.S. Publication No. 20030059903), it is noted that the specification in this application discloses practicing the claimed process for the production of L-threonine with an E. coli cell as one of the preferred embodiments. See paragraphs 16-32 and Example 4. As such, claims 1, 4-5 and 9 of the instant application would be considered obvious over claims 12-14 of copending Application No. 10/114048. With regard to copending Application No. 10/114073 (U.S. Publication No. 20030049803), it is noted that the specification in this application discloses practicing the claimed process for the production of L-threonine with an E. coli cell as one of the preferred embodiments. See paragraphs 16-32

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and Example 4. As such, claims 1, 4-5 and 9 of the instant application would be considered obvious over claims 12-14 of copending Application No. 10/114073.

***Conclusion***

26. No claim is in condition for allowance.

27. Applicant's amendment of claims 1-2, 4-7, 9 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

28. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 872-9306. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. **NO DUPLICATE COPIES SHOULD BE SUBMITTED**, so as to avoid the processing of duplicate papers in the Office.

29. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through

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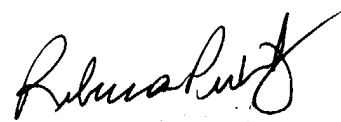
Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1234.

Delia M. Ramirez, Ph.D.  
Patent Examiner  
Art Unit 1652

DR  
April 5, 2004



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